

## University of Dundee

### Education, education, education

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1    **Education, education, education – now more than ever?**

2

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19

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21

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## 25    **Introduction**

26    A whole generation of young scientists and medical doctors enthusiastically entered the field of assisted  
27    reproduction and infertility treatment after the birth of the first *in vitro* fertilized (IVF) child Louise Brown in  
28    1978. A new paradigm for treating infertility opened and created unprecedented room for research and  
29    development. Indeed, the first years of the IVF era was characterised by a huge research effort  
30    understanding follicular development including ovarian stimulation and developing robust methods in the  
31    laboratory. Thus, many young clinicians and scientists found a significant career opportunity in the field.  
32    Their efforts and successes resulted in a logarithmic increase in activity. The SART register in USA have  
33    reported that the US had around 25 clinics performing a few thousands cycles annually in 1985, which  
34    today has risen to a little less than 400 clinics doing more than 200,000 cycles (SART, 2015). It is estimated  
35    that currently over 5 million IVF children have been born worldwide contributing significantly to the next  
36    generation (Fauser et al, 2013). Several of the clinicians and scientists who entered the field in the 1980'ties  
37    have been leading figures in IVF treatments but now 30-40 years later they have or are about to retire. This  
38    implies that the profession faces a massive transgenerational transition. This in itself calls for a strong  
39    educational effort of the new and coming generations, but a number of other factors also highlight the  
40    need for continued and expanded education in the field of reproduction.

41

## 42    **The IVF era: Standardizing treatments**

43    Whereas initially the emphasis was on basic research and development of the IVF technology, focus has  
44    during the past decades generally switched to optimising treatment outcome including standardisation and  
45    consolidating of procedures used clinically (De los Santos et al., 2016). This has resulted in improved  
46    reproductive outcome and more efficacious treatment modalities. The introduction of standardised  
47    operation procedures has stabilised results for most fertility clinics and currently many clinics perform with  
48    stable pregnancy rates. However, overall success rates have only shown modest increases in the last  
49    decade suggesting that continued increase in successful treatments is unlikely to derive from new and

50 different stimulation protocols and further standardisation of protocols and laboratory procedures. The  
51 above notwithstanding, success rates are still modest. According to recent ESHRE and ASRM reports a  
52 delivery rate of ~35 percent per cycle depending on patient selection (Calhaz-Jorge et al., 2017; SART,  
53 2015). There is a growing understanding that a continued and expanded research effort is mandatory to  
54 continue an improvement of treatment outcome.

55 Since the field started in early 1980'ties, the business model for infertility treatment has dramatically  
56 changed from being mainly a public-sector activity to more private sector involvement; in 2016 almost 60%  
57 of all IVF and ICSI treatment in Denmark was performed in private clinics despite public funding for patients  
58 below the age of 40 years (Sundhedsdatastyrelsen, 2016). This has necessarily resulted in an increased  
59 focus on efficient clinical services and less focus on development of new techniques and improved  
60 understanding of the underlying physiological processes (Spencer et al., 2016). However, an improved  
61 understanding of the physiological and molecular requirements for successful follicular development,  
62 oocyte maturation and sperm selection is widely acknowledged, but currently there is a limited effort to  
63 secure knowledge transfer to the young generations and for continued education.

64 In this context it is interesting to notice that a wave of consolidation among fertility centres has taken place  
65 in recent years in which many private fertility clinics are sold to larger consortiums usually comprising  
66 several clinics in several different countries (Sydney Morning Herald, 2008; 2013; 2015). These consortia  
67 often establish a central research and development unit to serve all member clinics. In the US, investors are  
68 transforming an industry that has long been dominated by standalone clinics so much so that in the USA  
69 the top five largest fertility chains now account for more than 16% of the marked share (SART, 2015).  
70 However, as yet it is not clear to what extend these units will contribute substantially to the basic science  
71 development required to advance new procedures with significant clinical impact. In addition, a lot of  
72 smaller private fertility clinics contribute only to a minor extent to the education of new clinicians and  
73 scientists, which with the increased development in the private sector potentially exacerbates the  
74 educational gap.

75 Despite innovations in assisted reproductive technology (ART) such as intracytoplasmic sperm injection  
76 (ICSI), preimplantation genetic diagnostic (PGD), and stem cell research the massive task of effectively  
77 treating women at an advanced age is still unresolved. With the substantial postponement of childbearing  
78 seen particularly in the European countries (Mills et al, 2011) and the increase in infertile couples seeking  
79 help to have a child (Kupka et al., 2016; SART, 2015), the field of reproductive sciences is facing an  
80 unprecedented challenge in developing new techniques to individualize and advance treatments for  
81 infertility. Many of the potential new treatments that are to be developed will require a multidisciplinary  
82 approach with several areas of expertise involved – often skills which do not normally participate in the  
83 reproductive medicine arena. Examples of such new areas include *in vitro* follicle activation with activation  
84 of specific intracellular signalling pathways (Kawamura et al., 2013), culture of human preantral follicles on  
85 suitable scaffolds (Yin et al., 2016a; Laronda et al., 2017; McLaughlin et al., 2018), *in vitro* maturation of  
86 immature human oocytes (Yin et al., 2016b), generation of artificial gametes from stem cells (Hikabe et al.,  
87 2016), understanding *in vitro* meiosis, understanding and improving sperm quality (Barratt *et al.*, 2017) etc.  
88 In order to facilitate an effective and orderly translational transition into the clinic a substantial educational  
89 effort in broad areas of reproduction will be required.

90

91 **The missing links to a new generation of reproductive scientists**

92 Other medical professions may inspire our field on how to potentially improve and advance the educational  
93 effort. For instance, in the area of neuropathology PhD students are required to follow 10 obligatory  
94 courses and to pass an EU-course offered by the European Confederation of Neuropathological Societies  
95 (Euro-CNS) in order to obtain their degree. Moreover, Euro-CNS has established several specialized  
96 scientific and clinical programs to their European members on both junior and senior level to facilitate the  
97 exchange of scientific information between members and to help clinicians and researchers to stay up to  
98 date with the latest advances within their field. Further, the Federation of European Neuroscience Societies

99 (FENS) representing 42 European countries conducts courses and meetings to promote excellence in  
100 neuroscience research (EAN, 2018).

101 Another initiative recently launched is the UK based Medical Research Foundation national PhD training  
102 programme in anti-microbial resistance research. This innovative national programme will train 150 new  
103 researchers to explore ways to tackle anti-microbial resistance, one of the greatest emerging threats to  
104 human health and will provide a strong educational and networking platform, which will strengthen the  
105 UK's research capacity overall during education. Importantly, an alumni platform for continued interaction  
106 after PhD graduation is also included (University of Bristol, 2018).

107 These programmes are obviously expensive undertakings but perhaps international societies such as ESHRE  
108 and ASRM could lead similar initiatives in our field and explore the options for a much more detailed and  
109 comprehensive educational effort.

110 On a practical level the professions attitude towards participation in congresses and educational activities  
111 should be re-evaluated. Often young researchers are required to submit an abstract to a conference in  
112 order to be supported financially. Most conferences understand this policy and accept most -- if not all --  
113 abstracts. Unfortunately, this does not always result in a high-quality peer-reviewed paper and may serve  
114 only as an entrance ticket for participation (Lensen *et al.*, 2017). Such a policy does not encourage senior  
115 researchers to act as reviewers and may in the long term reduce the quality of the reviewing process.  
116 Further, the abstract reviewing process is often not clear to neither those who submit an abstract and even  
117 to those who evaluate abstracts. This strategy does not support a strong and thorough research  
118 involvement from young clinicians and scientists and is in some aspects counterproductive to stimulate  
119 new substantiated ground-breaking research.

120 Moreover, in the early years of the IVF era the pharma industry had minimal restrictions on supporting  
121 participation in scientific conferences and symposia. Many young scientists and clinicians at that time  
122 benefitted and received a significant training and education due to support from the pharma industry,  
123 which to a large extent has disappeared today.

124 Additional challenges include the legal and regulatory structure for training in the field. For example, the  
125 recognition of clinical embryology, which is now developing into an area of its own right with highly skilled  
126 competences. This is not recognised in several countries, either educationally or legally and makes it less  
127 likely that highly skilled persons will persuade a career in the field of reproduction (Kovačič et al., 2015).  
128 These changes, amongst others, have led to a gap in the education of young scientists and clinicians. There  
129 is a profound educational need to improve basic skills of the next generation to be able to take infertility  
130 and treatment to the next level, improve clinical practise and widen the use of ART and make it more  
131 accessible to larger population groups.

132

### 133 **Multi-disciplinary educational platforms are needed**

134 Although this educational challenge is widely recognised, it is interesting to appraise how we are currently  
135 addressing it. . Large professional organisations like ESHRE and ASRM indeed undertake a lot of educational  
136 activities including for example a one-and-a-half-day special interest group workshop that often dive into a  
137 narrow area and provide an update on the current knowledge. Other arenas are well catered for. For  
138 example, training of embryologists and nurses where there are a plethora of courses and an examination  
139 system. However, in general these programmes are mainly centred on clinical activities and provide to a  
140 lesser extent a broader knowledge base from which basic science-oriented research can benefit. A  
141 fundamental question is how we best train our new MD/PhD students?

142 The ReproUnion network is an EU- and local funded multi-disciplinary collaboration between 14 public  
143 fertility clinics and several basic science-oriented laboratories in the Capital Region of Copenhagen in  
144 Denmark and the Skaane Region in Sweden. To date it has educated 25 PhD-students. This network has  
145 provided 4 different PhD-courses centred on basic science in reproductive biology, ART procedures, male  
146 fertility and epidemiological studies with reproductive medicine. ReproUnion support the ReproYoung  
147 association – a network of young researchers working in the field of reproduction and infertility.  
148 ReproYoung has facilitated inter-laboratory collaborations, and hosted several International ReproYoung

149 conferences, where all participants are required to present their work and have feed-back from other  
150 young colleagues and senior researchers. These activities, together with monthly education seminars,  
151 where the PhD-students present their work combined with senior lectures, provides a new type of  
152 educational platform with a knowledge base that is able to sustain a larger collaborative effort within the  
153 area of reproductive medicine. Another inter-sectorial and multidisciplinary network has recently been  
154 established - 'GrowSperm' which aims to train and coach young scientists in the field of male reproduction,  
155 and comprises several public and private EU partners.

156 However, the educational skills of hands-on laboratory training, where students learn specific procedures  
157 by actually doing them are still missing in the educational programme of ReproUnion. In the US they have  
158 overcome this hurdle with the Frontiers in Reproduction (FIR) course. FIR is a very successful and world-  
159 renowned programme in reproductive biology held annually since 1998 at the Marine Biological Laboratory  
160 (MBL) in Woods Hole, Massachusetts. The 6-week summer course represent a unique high-quality training  
161 experience comprising daily laboratory exercises, informal seminars, one-on-one tutorials, and lectures in  
162 the morning and evening by highly experienced faculty in the field. The FIR course is designed for scientists-  
163 in-training who seek to improve their knowledge and experimental skills in order to pursue a career in  
164 reproductive sciences, and a 10-year follow-up survey performed on former attendees has recently  
165 confirmed the overall significant positive impact that the course has had on the training and upward career  
166 trajectory of the participants (Ascoli et al., 2016). Moreover, the success of the course highlights the  
167 excellent networking opportunities and research collaborations within and between attendees and faculty  
168 which cannot easily be duplicated by any online e-learning system. The efficacy and impact of physical  
169 interactions and personal communication should not be underestimated, and the inspirational and passion-  
170 driven lessons from pioneers in the field are fundamental to these learning experiences.

171 The FIR course serves as a good example of what can be accomplished with this type of training platform  
172 and is an approach that needs to be complemented and expanded with a potential European counterpart  
173 to significantly impact the advances in the reproductive sciences.



174 Currently there is enormous interest in new educational methods and how best to educate future  
175 generations of scientists and clinicians (Bosch et al., 2017). In reproductive biology we also need to take a  
176 fresh look at our current programs and evaluate if they are fit for the education of a new generation of  
177 PhD/MD in the field.

178

## 179 **Conclusion**

180 For half a century medical professionals have been trained and educated to standardize and streamline  
181 ART, but current treatment has reached a plateau in success rates and costs. We are facing a new era in  
182 which research and development is absolutely fundamental to advance reproductive sciences. A new  
183 generation of reproductive scientists needs to be educated in a more structured, broader and purposeful  
184 way than current platforms are providing. Multi-disciplinary educational platforms are required to advance  
185 the research and provide a more fully equipped educational package for young researchers in the field.  
186 Today's trends in society calls for 'thinkers' – not merely technicians/clinicians – and we need to take  
187 responsibility for the next generation in more than one way.

188

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198

199    **Conflict of interest**

200    C.Y.A is the editor-in-chief of the Reproduction section of Frontiers in Endocrinology and has received  
201    lecturing and consulting fees from Merck, Ferring, Merck-Serono and IBSA.

202    C.L.R.B is the editor-in-chief of Molecular Human Reproduction and Chair of the World Health Organisation  
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205    S.G.K. is chairman of ReproYoung and has received lecturing fees from Merck and IBSA.

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